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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/31/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	Application No. 09/720,326	Applicant(s) SATO ET AL.	
	Examiner Karen A. Canella	Art Unit 1642	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 29 December 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL on the same KAC 3/28/05

2. ☒ The reply was filed ~~after the~~ date of filing a Notice of Appeal, but prior to the date of filing an appeal brief. The Notice of Appeal was filed on *29 December 2004*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☒ They raise the issue of new matter (see NOTE below);
   (c) ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: *none*.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1, 4, 6, 9-16, 19-21, 33*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☒ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☐ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

Karen A. Canella

KAREN A. CANELLA PH.D
PRIMARY EXAMINER

The rejection of claims 1, 4, 9, 10, 12, 13-15, 19, 20 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seger et al (US 5,494,806) in view of Potts (Diseases of the Parathyroid gland and other Hyper- and Hypocalcemic Disorders, In: Harrison's principles of Internal Medicine, 12th Edition, pages 1902-1915, IDS reference) and Schlom (In: Molecular foundations of Oncology, Samuel Broader, Ed, 1991, pages 95-134) is maintained for reasons of record.

Seger et al (U.S. 5,494,806) teach a method for rapidly intervening in a patient exhibiting hypercalcemia comprising the administration of antagonists of PTHrP (column 24, lines 35-41). Seger et al teach that such antagonists include compounds which interfere with the PTH receptor-mediated activation and that the appropriate antibody antagonist or peptide antagonist is administered at a dosage that provides adequate competition for PTHrP binding to the PTH receptor and that this will correspond to the dosage sufficient to lower the calcium level to below 10 mg/dl (column 24, lines 41-51), thus fulfilling the specific embodiment of treating a patient susceptible to hypercalcemic crisis associated with impaired consciousness comprising administering to said patient a anti-PTHrP antibody inhibiting the binding between PTHrP and the PTH receptor and allowing the antibody to inhibit the binding of PTHrP to the PTH receptor and decreasing a blood calcium level to effectively treat said patient. Seger et al teach that the antibody can be formulated in a carrier (column 24, lines 45-46) thus fulfilling the specific embodiment of claims 10 and 20. Seger et al teach that treatment may be repeated as necessary for long term maintenance of acceptable calcium levels of less than 10.1 mg/dl (column 24, lines 52-55) thus fulfilling the specific embodiment of claims 1 and 13 specifying that the blood calcium level be decreased to below 15 mg/dl. Seger et al teach that the antibodies and other compounds of the invention are useful for the treatment of disorders characterized by the interaction between a cell receptor of the invention and a ligand (column 23, lines 25-40). Seger et al teach that hypercalcemia mediated by PTHrP results from humoral hypercalcemia of malignancy (column 23, lines 46-47) thus fulfilling the specific embodiment of claims 1 and 13 drawn to a malignant tumor. Seger et al teach that compounds, including antibodies and polypeptide, may be screened for their agonistic or antagonistic properties using the cAMP accumulation, intracellular calcium, and/or inositol phosphate assays as specifically described (columns 22, line 65-column 23, line 22). Seger et al do not specifically teach administering a humanized anti-PTHrP antibody or the treatment of hypercalcemic crises wherein the patient exhibits at least one of coma or cardiac arrest.

Potts teaches that severe hypercalcemia, usually defined as 15 mg/dl or above is a medical emergency, and that coma or cardiac arrest can occur when serum calcium levels are at 15 to 18 mg/dl or higher. Thus, the art recognizes that severe hypercalcemia results in coma or cardiac arrest.

Schlom teaches that in all of the previous reported human trials in which non-immunosuppressed patients were treated with multiple doses of murine antibodies only the first and perhaps the second dose of said antibody was efficiently reaching the tumor site due to the HAMA response. Schlom teaches that it is unrealistic to assume that just one or two administrations of any anti-cancer therapeutic would be effective. Schlom teaches that the answer to this problem is the humanization of the murine antibodies (pages 97-98, bridging paragraph). Schlom also teaches that F(ab')2 or Fab' fragments also help reduce the HAMA response (page 119 second column, lines 16-17 under the heading "Single Chain Antigen Binding Proteins). Schlom also teaches that scFv although comparable in binding affinity to FAb' have a more rapid plasma clearance than the Fab' fragment resulting in a greater tumor to tissue ratio. Schlom also points out that the small size of the scFv improves the capacity for penetration through the tumor mass.. Schlom also points out that scFv are easier to make than F9ab')2 of Fab' fragments.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to treat a patient undergoing hypercalcemic crisis wherein said crises was manifest by coma or cardiac arrest or blood calcium levels in excess of 15 mg/dl by the administration of a humanized anti-PTHrP antibody which is an antagonist of PTHrP binding to the PTH receptor in order to lower blood calcium to normal levels. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Seger et al on the method of treating patients needing immediate intervention because elevated serum calcium level can be fatal; and the teachings of Potts regarding the risk of coma or cardiac arrest in individual having serum calcium levels of 15 mg/dl to 18 mg/ dl or higher. It would also be obvious to use a fragment of the antibody such as scFv for maximum penetration into the tumor vasculature. Further, one of skill in the art would be motivated to maintain the decrease in blood calcium levels in order insure that the patient was stabilized.

The rejection of claims 1, 4, 9-15, 19-21 and 33 under 35 U.S.C. 103(a) as being unpatentable over Seger et al (US 5,494,806) and Potts (Diseases of the Parathyroid gland and other Hyper- and Hypocalcemic Disorders, In: Harrison's principles of Internal Medicine, 12th Edition, pages 1902-1915) and Schlom (In: Molecular foundations of Oncology, Samuel Broader, Ed, 1991, pages 95-134). as applied to claims 1, 4, 9, 10, 12, 13-15, 19, 20 and 33 above, and further in view of Gristina et al (5,681,565) is maintained for reasons of record. The specific embodiments of claims 1, 4, 9, 10, 12, 13-15, 19, 20 and 33 and the teachings of Seger et al, Potts and Schlom which render obvious said embodiments are set forth above. None of the cited reference specifically teach the antibody bound to the carrier PEG.

Gristina et al teach that antibodies can administered in a cream or ointment carrier such as oleaginous bases or polyethylene glycol for in situ use (column 5, lines 3-21).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention to use PEG as a carrier. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Grishina et al on the effectiveness of PEG as a carrier for in situ administration of antibodies.

The rejection of claims 1, 6, 9, 10, 13, 16, 19, 20 and 33 under 35 U.S.C. 103(a) as being unpatentable over the abstract of Sato et al (WO 9813388, IDS reference) in view of Potts (Diseases of the Parathyroid gland and other Hyper- and Hypocalcemic Disorders, In: Harrison's principles of Internal Medicine, 12th Edition, pages 1902-1915) is maintained for reasons of record.

Claims 6 and 16 embody the methods of claim 1 and 13, respectively, wherein the antibody is humanized antibody deposited under the Accession Number FERM BP-5631, The specification teaches that the humanized monoclonal antibody #23-57-137-1 was deposited under the Accession Number FERM BP-5631. CHECK DEPOSIT

The abstract of Sato et al teaches the humanized #23-57-137-1 monoclonal antibody. The abstract teaches that the humanized antibody can be used to treat hypercalcemia and other disorders caused by cancer. The abstract does not teach that the humanized #23-57-137-1 monoclonal antibody would inhibit the binding of the PTHrP and the PTH receptor, however, the antibody is identical to the specific embodiment of claims 6 and 16, therefore said antibody must have the inherent characteristic of inhibiting the binding of PTHrP to the

PTH receptor. The abstract does not specifically teach drug-resistant hypercalcemic crisis associated with coma and cardiac arrest of a blood calcium level in excess of 15mg/dl.
Potts teaches that severe hypercalcemia, usually defined as 15 mg/dl or above is a medical emergency, and that coma or cardiac arrest can occur when serum calcium levels are at 15 to 18 mg/dl or higher. Potts teaches that the humoral mediator of malignancy associated hypercalcemia is PTHrP. Potts teaches that this mediator competes with PTH for occupancy of the PTH receptor and induces hypercalcemia in test animals, and that the data indicate that PTHrP acts through activation of the PTH receptor (page 1908, first column, lines 2-9).
It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention to use the #23-57-137-1 antibody in the treatment of hypercalcemic crises. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Potts who describe hypercalcemic crises as resulting in coma or cardiac arrest. One of skill in the art would be motivated to provide an agent which would bind to PTHrP and decrease the binding of PTHrP to the PTH receptor because Potts teaches that it is the activation of the PTH receptor by PTHrP that is responsible for hypercalcemia. One of skill in the art would be motivated to combine the teachings of Potts with the teachings of Sato et al because the abstract of Sato et al states that the #23-57-137-1 antibody, which binds to PTHrP, can be used in the treatment of hypercalcemia. One of skill in the art would readily conclude that the that #23-57-137-1 would act by inhibiting the binding of PTHrP and the PTH receptor. Without being able to inhibit the binding of the PTHrP to the PTH receptor, the antibody would not be effective in the treatment of hypercalcemia, and the effect would not be consistent with the teachings of Sato et al, that the antibody is useful in treating hypercalcemia.

The rejection of claims 1, 4, 6, 9, 10, 12, 13-16, 19, 20 and 33 under 35 U.S.C. 103(a) as being unpatentable over the abstract of Sato et al (WO 9813388 and Potts (Diseases of the Parathyroid gland and other Hyper- and Hypocalcemic Disorders, In: Harrison's principles of Internal Medicine, 12th Edition, pages 1902-1915) as applied to claims 1, 6, 9, 10, 13, 16, 19, 20 and 33 above, and further in view of Schlom (In: Molecular foundations of Oncology, Samuel Broader, Ed, 1991, pages 95-134) is maintained for reasons of record.

The combination of Sato et al and Potts renders obvious claims for the reasons set forth above. Claims 4 and 14 embody the methods of claims 1 and 13, respectively wherein the patient is administered at least one fragment of the humanized anti-PTHrP antibody. Claims 5 and 15 embody the method of claims 4 and 14, respectively wherein the fragment is chosen from at least one of Fab, scFV, F(ab')2 and Fv. Neither the abstract of Sato et al nor Potts et al teach the administration of antibody fragments.
Schlom teaches that F(ab')2 or Fab' fragments also help reduce the HAMA response (page 119 second column, lines 16-17 under the heading "Single Chain Antigen Binding Proteins). Schlom also teaches that scFv although comparable in binding affinity to Fab' have a more rapid plasma clearance than the Fab' fragment resulting in a greater tumor to tissue ratio. Schlom also points out that the small size of the scFv improves the capacity for penetration through the tumor mass.. Schlom also points out that scFv are easier to make than F9ab')2 of Fab' fragments.
It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention to use fragments of the #23-57-137-1 antibody in the treatment of hypercalcemic crises. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Schlom et al who point out that antibody fragments such as Fab' result in a greater tissue to tumor ration and that scFv have a greater ability to penetrate tumor vasculature.

The rejection of claims 1, 4, 6, 9, 10, 12, 13-16, 19, 20 and 33 under 35 U.S.C. 103(a) as being unpatentable over the abstract of Sato et al (WO 9813388) and Potts (Diseases of the Parathyroid Gland and Other Hyper- and Hypocalcemic Disorders, In: Harrison's principles of Internal Medicine, 12th Edition, pages 1902-1915) and Schlom (In: Molecular foundations of Oncology, Samuel Broader, Ed, 1991, pages 95-134).as applied to claims 1, 4, 6, 9, 10, 12, 13-16, 19, 20 and 33 above, and further in view of Gristina et al (US 5,681,565) is maintained for reasons of record.
Claims 10 and 20 embody the methods of claims 1 or 4, or claims 13 or 14, respectively, wherein the antibody is bound to a carrier. Claims 11 and 21 specify that the carrier of claim 31 is PEG. Neither of the prior art references of the Sato et al abstract, nor Potts, nor Schlom teach antibodies bound to PEG as a carrier.
Gristina et al teach that antibodies can administered in a cream or ointment carrier such as oleaginous bases or polyethylene glycol for in situ use (column 5, lines 3-21).
It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention to use PEG as a carrier for the #23-57-137-1 antibody. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Grishina et al on the effectiveness of PEG as a carrier for in situ administration of antibodies.

The rejection of claims 1, 4 and 6-16, 19-21 and 33 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 126-136 and 138 of copending Application No. 09/269,332 in view of Potts (Diseases of the Parathyroid gland and other Hyper- and Hypocalcemic Disorders, In: Harrison's principles of Internal Medicine, 12th Edition, pages 1902-1915) and Schlom (In: Molecular foundations of Oncology, Samuel Broader, Ed, 1991, pages 95-134) is maintained for reasons of record.

Claims 126-136 and 138 of the '332 application teach the administration of a polypeptide comprising an L chain V region of a humanized antibody comprising an amino acid sequence selected from the group consisting of SEQ ID NO:48-51 or 52-55.

Potts teaches that severe hypercalcemia, usually defined as 15 mg/dl or above is a medical emergency, and that coma or cardiac arrest can occur when serum calcium levels are at 15 to 18 mg/dl or higher.

Schlom teaches that F(ab')2 or Fab' fragments also help reduce the HAMA response (page 119 second column, lines 16-17 under the heading "Single Chain Antigen Binding Proteins). Schlom also teaches that scFv although comparable in binding affinity to FAb' have a more rapid plasma clearance than the Fab' fragment resulting in a greater tumor to tissue ratio. Schlom also points out that the small size of the scFv improves the capacity for penetration through the tumor mass.. Schlom also points out that scFv are easier to make than F9ab')2 of Fab' fragments.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to treat a patient undergoing hypercalcemic crisis wherein said crises was manifest by coma or cardiac arrest by carrying out the methods of claims 126-136 and 138 in order to lower blood calcium to normal levels. One of ordinary skill in the art would have been motivated to

do so with a reasonable expectation of success by the teachings of Potts regarding the risk of coma or cardiac arrest in individual having serum calcium levels of 15 mg/dl to 18 mg/ dl or higher. It would also be obvious to use a fragment of the antibody such as scFv for maximum penetration into the tumor vasculature.

It is noted that claims 126-136 and 138 do not specify the administration of a humanized #23-57-137-1 antibody. However, said antibody is included in the genus of antibodies upon which the '332 method claims depend. The Office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).
This is a provisional obviousness-type double patenting rejection.

The rejection of claims 1, 4 and 6-16, 19-21 and 33 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 126-136 and 138 of copending Application No. 09/269, and Potts (Diseases of the Parathyroid gland and other Hyper- and Hypocalcemic Disorders, In: Harrison's principles of Internal Medicine, 12th Edition, pages 1902-1915) and Schlom (In: Molecular foundations of Oncology, Samuel Broader, Ed, 1991, pages 95-134) as applied to claims 22-30 above and in further view of Gristina et al (US 5,681,565) is maintained for reasons of record.
Gristina et al teach that antibodies can administered in a cream or ointment carrier such as oleaginous bases or polyethylene glycol for in situ use (column 5, lines 3-21).
It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention to use PEG as a carrier for the antibodies in method claims 126-136 and 138 of application '322. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Grishina et al on the effectiveness of PEG as a carrier for in situ administration of antibodies.

Applicant has presented a declaration to aver that the administration of an antibody which inhibts the binding between PTHrP and a reetpro thereof produces unexpected results in the treatment of hypercalcemic crisis in thatr said antibody is able to regulate the calcium level of a pateint and effectively treat hypercalcemic crises in contrast to traditional treatments for hypercalcemia. This has been considered but not found persausvie in light of thje teachings of Seger et al on specfically inhibiting the PTHrP via and antagonistic antibody which inhibits the binding of PTHrP to the PTH receptor. The only teachings missing from Seger et al are the adminsitration of a humanized rather than murine antibody, which is made up for by the teachings of Schlom and the characterization of hypercalcemic crises as encompassing coma or cardiac arrest, both of which are taught in the art to be manifestations of sever hypercalcemia as taught by Potts

The amendment of December 12, 2004 has attempted to introduce new claims 34-42, however, claims 35 which defines a hypercalcemic crrises as a blood calcium level that does not normalize after 24 hours of treatment and remain normal over at least 24 hours with one of the therapetuic agetnts chosen from biphosphonate, calcitonin, a steroid, phosphate buffer, physiiological saline, and furosemide lack adeuqate support in the specification and claims as filed. The specification contemplate on page 7, lines 2-6 ~~contemplate~~ that the adminsitration of the claimed "agent" can normlaize corrected serum calcium levels over 24 hours, preferably 3 days mor preferably 5 days....after the adminsitration of the "agent" does not provide support for the administration of the antibody to a patient previously ttreated, wherein said pateints blood calcium level did not remain normal after 24 hours of treatment with biphosphonate, calcitonin, a steroid, phosphate buffer, physiiological saline, and furosemide.

Applicant argues that the new rejections under 103(a) which were presetned in the office action of July 29, 2004 somehow did not result in compact prosecution. However, the subject matter that was rejected under 103(a) on July 29, 2004 was the same subject matter that was rejected under 103(a) in Feb 4, 2004. It was applicant's amenements to the claims to overcome the rejection under 112, 1st that led to the rejection under 103(a). Applicant was well aware of the subject matter which was rejected Feb 2004 and could understand that the amendment to the claims would result in subject matter that was the same as that previously rejected under 103(a) and canceled with claims 22-32. It is noted that subeject matter rejected for lack of enablement cannot be simultaneously rejected as obvious. Further, the rejection under 112, 1st Therefore the examiner did not belately reject claims 1, 4, 6, 9-16, 19-21 and 33 as being obvious when the claims at the time of the Feb 2004 rejection were not enabled under 112, first paragraph.

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
March 28, 2005